PHUSE 2021 Live Presentation

How ML-driven Automation Technology Can Overcome the Limitations of Double Programming

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Hugh Donovan - Former EVP clinical research services, Parexel

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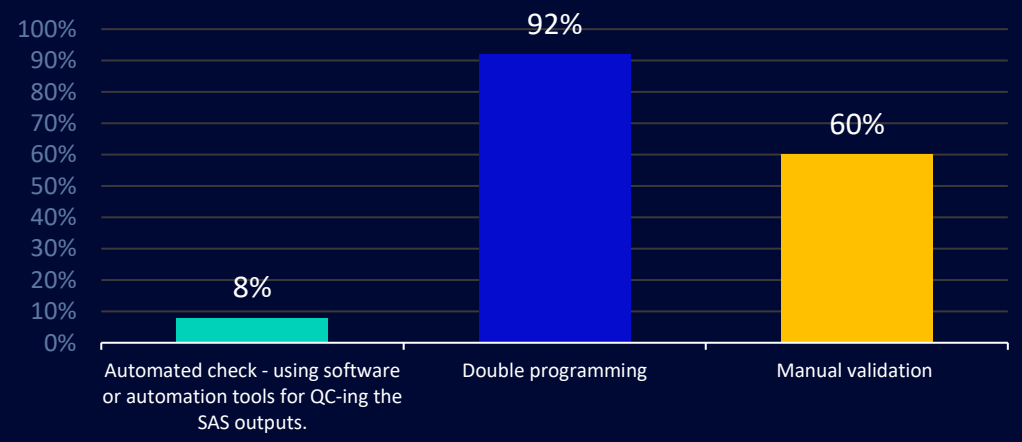
Topics

- Key Findings From a ‘Statistical Programming Output Validation Survey 2021’ - Hugh
- Double Programming Limitations - Hugh
- New Approaches - The Power of Automation - Ilan

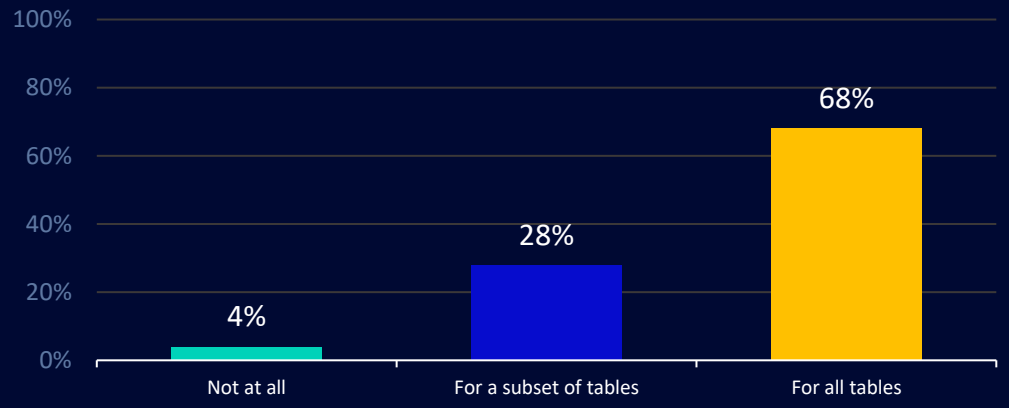
Key Survey Findings (1)

How do you QC the SAS outputs ahead of a submission (mark all relevant answers):



More than half of the respondents have manual validation

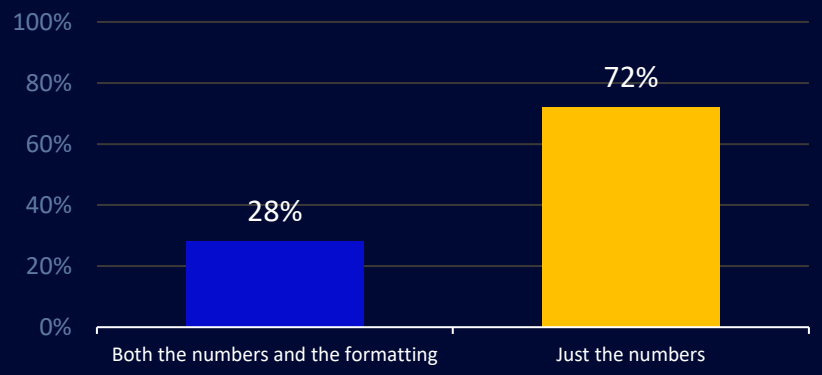
Do you or your provider use double programming in the production of tables?



Vast majority of companies still use double programming, at least for some tables

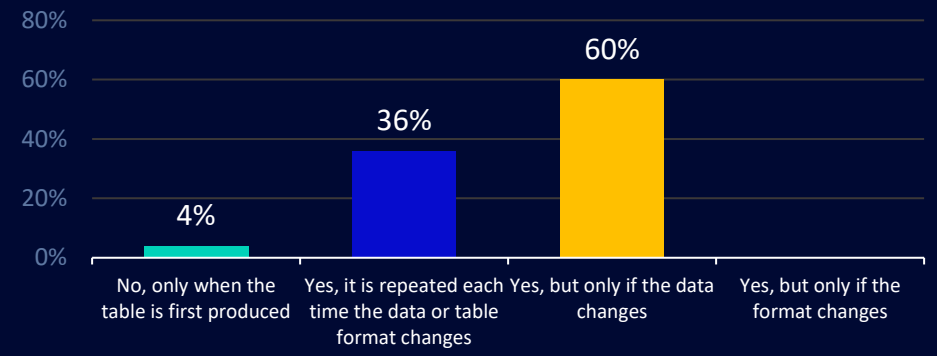
Key Survey Findings (2)

If double programming is used, are both the numbers and formatting reconciled or just the numbers?



Three quarters of respondents do not check table formatting, which undermines the value of double programming.

If double programming is used, is data reconciliation repeated?



64% of the time, the validation is not re-done if the format is changed

The Limitations of Double Programming

- It is not truly independent programming
- Although the numbers maybe the same, they may be wrong
- It typically involves a lot of manual checking
- Misinterpretation of the specifications
- It is typically only applied if the data changes, not if the format changes
- The double programming only works within a table

How to Apply ML Technology for Validating Outputs?

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Main Technical Challenges

Clinical outputs are digital files designed for the **human eye**

Main challenges:

1. There is no standard for clinical tables in the life sciences industry
2. Different digital data formats (TXT, RPT, HTML, RTF, PDF, Docx)
3. Data includes free text (design for the human eye)
4. No machine-readable standard format
5. Unstructured tables
6. Metadata is missing

Define Your Goals

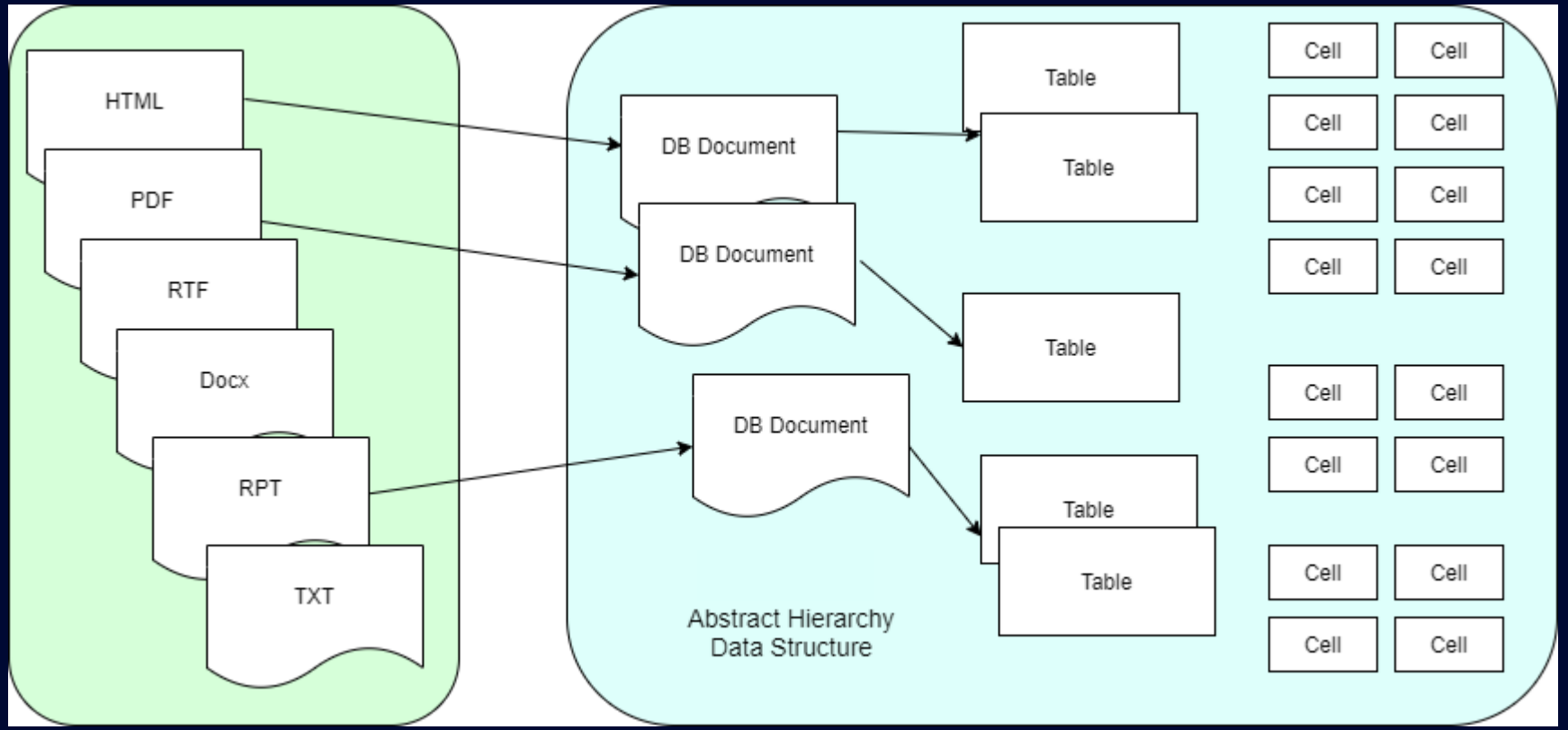
1. Accuracy sensitivity
2. What data type would you like to validate?
3. What kind of checks do you want to perform?
4. Get your ROI in place (Quality vs Cost vs Timelines)

Standardization

Develop algorithms to standardize your data that will support data type, outputs structure, clinical phase and TA.

Table Parsing

Parsing each format to convert it into a coherent, unified representation



Meta-Data Extraction

Extract meta-data automatically to enrich your data.

For example, data hierarchy, data type, etc.

Understanding the Content

Understand table data from:

- Headers that indicate cell content
- Table titles
- Table footnotes
- Table hierarchy

Example of a Post-Text table

Table 14.1.2.4
Overall Summary of Treatment Emergent Adverse Events (Safety Population)

	Drug A (N=119)	Drug B (N=117)	Total (N=236)
Any AEs	73 (61.3%)	88 (75.2%)	161 (68.2%)
0-4 Weeks:			
Any TEAEs	75 (63.0%)	85 (72.6%)	156 (66.1%)
Serious TEAEs	3 (2.5%)	17 (14.3%)	7 (5.9%)
Drug-Related TEAEs	17 (14.3%)	27 (23.1%)	44 (18.6%)
Discontinued due to TEAEs	7 (5.9%)	9 (7.7%)	16 (6.8%)
4-8 Weeks:			
Any TEAEs	48 (40.3%)	38 (32.5%)	86 (36.4%)
Serious TEAEs	1 (0.8%)	3 (2.6%)	4 (1.7%)
Drug-Related TEAEs	12 (10.1%)	20 (17.1%)	40 (16.9%)
Discontinued due to TEAEs	3 (2.5%)	4 (3.4%)	7 (3.0%)
8-12 Weeks:			
Any TEAEs	25 (21.0%)	20 (17.1%)	45 (19.1%)
Serious TEAEs	0 (0.0%)	1 (0.9%)	1 (0.4%)
Drug-Related TEAEs	7 (5.9%)	5 (4.3%)	12 (5.1%)
Discontinued due to TEAEs	1 (0.8%)	1 (0.9%)	2 (0.8%)
0-12 Weeks:			
Any TEAEs	83 (69.7%)	93 (79.5%)	176 (74.6%)
Serious TEAEs	3 (2.5%)	7 (6.0%)	10 (4.2%)
Drug-Related TEAEs	28 (23.5%)	30 (25.6%)	58 (24.6%)
Discontinued due to TEAEs	11 (9.2%)	14 (12.0%)	25 (10.6%)

Note: Subject 003-005 was randomized to Drug A but received Drug B in error.
The Safety Population is all subject who received at least one does of medication.
Any AE is any adverse event that began after the beginning of the screening period.
Any TEAE is any adverse event that began after the first dose.
Source Data: adae Table Generation: 18MAY2021 (15:51)
(Cutoff date : 03MAY2021 Snapshot date : 03MAY2021)

Presentation in the Database

SAS File Output

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VERIFY

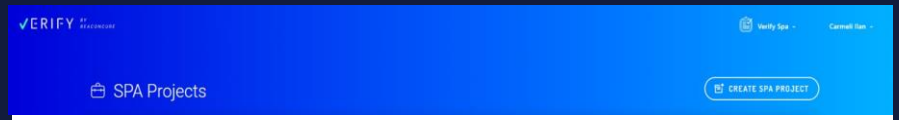

Table number: 14.1.2.4
Table title: Overall Summary of Treatment Emergent Adverse Events (Safety Population)
Population: Safety
Table category: adverse events
Cell type: Data cell
Cell value: 3
Data type: number, decimal
Column Headers: [Drug B N=117]
Rows headers: [4-8 weeks, Serious TEAEs]
Arm treatment: Drug B
Subjects denominator (N): 117
Time: 4-8 weeks
AE category: Serious
Cutoff date: 5.3.2021
Snapshot date: 5.3.2021

Generalized Validation Checks

1. Review your list of checks for validating the outputs
2. Make sure that your data support such checks
3. Break complex and large checks to small pieces
4. Generalize your checks to support all studies and TA

Feedback from Clinical SME

Make sure to work closely with your SME.

The SMEs will be a very important piece in the automation efforts.

Example of Check Based ML

The ‘Received at least one dose’ population is not consistent between tables

Table 14.1.1.2

Subject Disposition

	Drug A	Drug B	Total
Randomized	119	117	236
Received at least one dose	118	118	236
Completed 4 weeks	89	87	176
Completed 8 weeks	82	75	157
Completed Study	75	69	144
Per Protocol	48	39	87

Note: Subject 003-005 was randomized to Drug A but received Drug B in error.
Cutoff date: 03MAY2021 Snapshot date: 03MAY2021

Table 14.1.1.4

Demographics (Received at Least One Dose)

	Drug A	Drug B	Total
Gender			
Male	60 (51.3%)	60 (50.8%)	120 (50.8%)
Female	59 (48.7%)	57 (49.2%)	116 (49.2%)
Age			
<18	1 (0.8%)	0	1 (0.4%)
18-30	34 (28.6%)	33 (28.2%)	68 (28.8%)
31-45	36 (30.3%)	37 (31.6%)	73 (30.9%)
46-65	46 (38.7%)	47 (40.2%)	93 (39.4%)
>65	1 (0.8%)	0	1 (0.4%)
Weight			
n	118	115	233
Mean	75.12	75.34	77.79
SD	7.34	7.52	7.74
Median	77.8	78.1	77.9
Min	62	67	62
Max	88	89	89

Note: Subject 003-005 was randomized to Drug A but received Drug B in error.
Cutoff date: 03MAY2021 Snapshot date: 03MAY2021

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The Benefits of Using a Software Based on ML

'Automation of the validation process, supported by ML, reduces complexity, increases quality, streamlines business processes & workflows, and increases efficiency'

THANK YOU

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